Applicants are submitting herewith a stamped postcard indicating that 51 references, including 41 foreign references and 10 other references, were received by the mailroom at the Patent Office. Therefore, the Patent Office has all of the references identified on the PTO Form 1449 and it was error not to consider same.

If for some reason the Examiner still requires copies of any of these references, Applicants respectfully request that the Examiner contact Applicants' undersigned attorney and copies of these references will be delivered by hand to the Examiner. Regardless, Applicants have done all that they can do to submit the requisite Information Disclosure Statement and copies of the references. This is a continuation application, all of the references were submitted in the parent application. Thus, the Applicants did not need to submit a second copy of the references. 37 C.F.R. § 1.98(d). The Patent Office requested a second copy of the references. Therefore, for the convenience of the Patent Office, Applicants supplied a second set of these references. Therefore, twice these references have been provided to the Patent Office. The fact that the references did not make it to the Examiner from the mailroom does not relieve the Patent Office from its obligation to consider same. In this regard, the Patent Office is required, pursuant to the rules, to review the references in the parent application.

Regardless, Applicants are submitting a still further Information Disclosure Statement with PTO Form 1449 once again bringing the references that were lined out to the attention of the Patent Office. The Patent Office is referred to the parent application for copies of the references. However, in the spirit of cooperation, should the Examiner require a still further set of the references, Applicants respectfully request that the Examiner contact the Applicants' undersigned attorney and a set will be hand carried to the Examiner.

With respect to the objection to Claims 6, 10 and 11 based on certain informalities, Applicants note that they have amended the claims as requested by the Examiner. Therefore, Applicants respectfully request that the objection be withdrawn.

Claims 1-16 stand rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,663,166 (*Veech*) or U.S. Patent No. 6,020,007 (*Veech 2*) in view of U.S. Patent No. 5,296,242 (*Zander*). In addition, Claims 1-5 stand rejected under 35 U.S.C. § 103 as being

unpatentable over an article to *Schambye* in view of *Zander*. Applicants respectfully submit that these rejections are not proper for the following reasons.

The claimed invention relates to an improved peritoneal dialysis solution and an improved method of combating metabolic acidosis in peritoneal dialysis patients by administering peritoneal dialysis solutions of the present invention.

As set forth in independent Claim 1, the peritoneal dialysis solution of the present invention includes a bicarbonate concentration of less than or equal to 30 mM/L, a carbon dioxide partial pressure that is less than 60 mmHg and at least one weak acid at a concentration between 15 mEq/L and approximately 20 mEq/L which is selected from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. Acetate is not one of the weak acids which is used in the solution of the present invention.

Claims 6 and 10 require the peritoneal dialysis solution to include dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a range from 20.0 to 30.0 mEq/L and a weak acid in a concentration from 10 to 20 mEq/L that is chosen from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate. The solution of Claim 6 also has a carbon dioxide partial pressure that is less than 60 mmHg. The solution of Claim 10 has a carbon dioxide partial pressure that is similar to the partial pressure of a normal subject's blood and further has a pH of 7.0 to 7.4.

The method of Claim 11 includes the step of administering to the patient a peritoneal dialysis solution that has a bicarbonate level and a carbon dioxide partial pressure that is substantially similar to that found in the patient's blood and which further includes dextrose, sodium, chloride, calcium, magnesium, bicarbonate in a concentration ranging from 20 to 30 mEq/L and a weak acid in a concentration ranging from 10 to 20 mEq/L.

Applicants will first address the rejection of independent Claim 1 and dependent Claims 2-5 under 35 U.S.C. § 103 as being unpatentable over *Schambye* and *Zander*.

In summary, the Office Action cites *Schambye* for the proposition that *Schambye* discloses peritoneal dialysis solutions having bicarbonate concentrations of 10-20 mM, lactate concentrations of 20.8-6.7 mM and a pH range from 7.0-7.4. Specifically, the Office Action cites a solution disclosed in *Schambye* having a bicarbonate concentration of 20 mM, a lactate concentration of 12.5 mM and a pH of approximately 7.2. This solution allegedly being "the least cytotoxic." The Office Action admits that *Schambye* does not disclose a CO_2 partial pressure but notes that *Schambye* discloses that "all examinations were carried out in a 40 mmHg CO_2 atmosphere." See the Office Action, pp. 4 and 5.

To supplement *Schambye* with respect to its lack of teaching of a carbon dioxide partial pressure, the final Office Action cites *Zander* which discloses that "preliminary research" reveals that dialysis solutions are particularly suitable if their pH value, bicarbonate concentration and CO_2 partial pressure correspond to physiological blood plasma values (*citing* column 2, lines 35-39 of *Zander*). The Office Action then cites the "physiological values" cited in *Zander* as having a pH of 7.4 +/- 0.05, a bicarbonate concentration of 24 mmole/l and a CO_2 partial pressure of 40 mmHg (*citing Zander* at column 2, lines 40-43).

Thus, the Office Action relies on *Schambye* as a primary reference because it discloses a peritoneal dialysis solution having a bicarbonate concentration range of 10-20 mM, a lactate concentration range of 6.7-20.8 mM and a pH range of 7.0-7.4. Because *Schambye* does not disclose a carbon dioxide partial pressure, the Office Action cites *Zander* as a supplemental reference even though the section of *Zander* cited (column 2, lines 35-54) does not suggest the incorporation of a weak acid into a peritoneal dialysis solution to provide the buffer qualities of the present invention. The only weak acid suggested by *Zander* appears at column 6, line 50 where *Zander* suggests an acetate concentration of 27.2 mmole/l.

Independent Claim 1 requires a peritoneal dialysis solution having a bicarbonate concentration of less than or equal to 30 mM/L, a carbon dioxide partial pressure of less than 60 mmHg and at least one weak acid at a concentration ranging from 15 mEq/L to about 20 mEq/L.

The weak acid is selected from the group consisting of lactate, pyruvate, citrate, isocitrate, cis-aconitase, α-ketoglutarate, succinate, fumarate, malate and oxaloacetate.

The Office Action relies upon *Schambye* as a primary reference because it teaches a peritoneal dialysis solution having a bicarbonate concentration of 10-20 mM, a lactate concentration of 6.7-20.8 mM and a pH ranging from 7.0-7.4.

However, *Schambye* does not address the problem of maintaining the acid-base balance of the patient. Instead, *Schambye* is directed toward the optimization of dialysis solutions with respect to their effect on normal human polymorphonuclear granulocytes *in vitro* without any consideration as to the ability of these solutions to maintain the acid-base balance in the patient or the ability of these solutions to correct the problem of metabolic acidosis associated with end stage renal disease. Thus, *Schambye* is not directed toward solving the same problem -- metabolic acidosis-- as the present invention.

Accordingly, because *Schambye* is not concerned with the acid-base balance of the patient, *Schambye* does not teach or suggest the use of a partial pressure of carbon dioxide nor does *Schambye* teach or suggest a partial pressure of carbon dioxide that is maintained by the presence of carbonic acid. As discussed above, the unique combination of the two buffers of the present invention provide a safe and effective dialysis solution that is not disclosed or suggested by any combination of *Schambye* and *Zander*.

While *Zander* does teach a dialysis solution with a carbon dioxide partial pressure of about 40 mmHg, a person skilled in the art of peritoneal dialysis would readily recognize that the solutions proposed by *Zander* would not be effective in maintaining the acid-base balance of dialysis patients.

Specifically, the "preliminary research" disclosed in *Zander* at column 2, lines 35-39, discloses a solution having a bicarbonate concentration and carbon dioxide partial pressure corresponding to physiological blood plasma values. However, column 2 of the *Zander* reference does not disclose the weak acid that is necessary as a second buffer because of the relatively low concentration of bicarbonate. The weak acid preferred by *Zander* is acetic

acid/acetate at a concentration of 27.2 mmole/l in the combined solution. The use of acetate in this high concentration has two problems.

First, it has been known for over 10 years that acetate damages the peritoneal membrane causing loss of ultrafiltration. See Faller and Marichal, "Loss of Ultrafiltration and Continuous Ambulatory Peritoneal Dialysis: A Role for Acetate", *Peritoneal Dialysis Bulletin*, Jan.-Mar. 1984 (Attached hereto as Exhibit A). Second, the acetate concentration (27.2 mmole/l) is too high. Applicants are submitting herewith the Declaration of Dr. Martis, attached hereto as Exhibit B that was submitted in the parent application. As set forth therein, by utilizing a weak acid concentration that is too high (27.2 mmole/l), *Zander* teaches a solution that is incapable of maintaining the acid-base balance. Hence, *Zander* fails to disclose a solution with a buffer content capable of maintaining the acid-base balance and because *Zander* promotes the use of acetate, one skilled in the art would not look to *Zander* for guidance in designing a peritoneal dialysis solution.

In contrast, the present invention provides a unique combination of two buffers (bicarbonate and a weak acid selected from a group that does not include acetic acid) which is both safe and effective. The safety and the efficacy of the solution of the present invention is established by the data presented in the Declaration of Dr. Martis. In contrast, a person skilled in the art of peritoneal dialysis will readily recognize that the solution proposed by *Zander* will lead to metabolic alkalosis and therefore is not suitable for use as a dialyzing fluid for long term maintenance dialysis. Further, *Zander* does not teach or suggest the ratio of the two buffers used in the present invention.

Thus, one skilled in the art would continue reviewing the *Zander* reference in search of a weak acid component. That weak acid component is listed at column 6, lines 47-52 where *Zander* discloses the use of acetate in a concentration of 27.2 mmole/L. As noted above, this weak acid concentration falls outside the scope required by Claim 1. Further, as noted in the Declaration of Dr. Martis, acetate damages the peritoneal membrane causing loss of ultrafiltration and therefore one skilled in the art upon reviewing column 6 of the *Zander* reference would discard the *Zander* reference.

Thus, *Zander*, with its high acetate concentration that exceeds the weak acid limit required by Claim 1, teaches away from the solution of Claim 1.

Further, because *Schambye* is not even directed toward the same type of solution as required by Claim 1, there is simply no reason or motivation to combine *Schambye* and *Zander* in the first place. In any event, upon reading *Zander*, one skilled in the art would be clearly discouraged from making the combination suggested by the Patent Office. Accordingly, the rejection of Claims 1-5 under 35 U.S.C. § 103 as being unpatentable over *Schambye* in view of *Zander* is improper and should be withdrawn.

The Office Action rejects Claims 1-16 under 35 U.S.C. § 103 as being unpatentable over *Veech* or *Veech 2* and further in view of *Zander*. *Veech 2* is apparently a continuation-in-part to *Veech*.

The Office Action relies upon the *Veech* references as the primary reference. To supplement the *Veech* references, the Patent Office cites *Zander* because it allegedly "discloses that using peritoneal dialysis solutions having a pH of 7.4 +/- 0.05, a bicarbonate concentration of 24 mmol/L and having a CO_2 partial pressure of 40 mmHg which corresponds to physiological blood plasma.

Independent Claims 1, 6 and 10 each require the bicarbonate concentration to range from 20 to 30 mEq/L. Independent Claims 1 and 6 each require the carbon dioxide partial pressure to be less than 60 mmHg. Independent Claim 10 requires the carbon dioxide partial pressure to be substantially similar to that of a normal person. Independent Claim 1 requires the weak acid to be present in a concentration ranging from 15 mEq/L while independent Claims 6 and 10 require the weak acid to be present in a concentration ranging from 10 to 20 mEq/L. Independent Claim 10 further requires the pH to range from 7 to 7.4.

Independent Claim 11 is directed toward a method of correcting metabolic acidosis in a peritoneal dialysis patient which includes the step of administering to a patient a peritoneal dialysis solution that has a bicarbonate level and a carbon dioxide partial pressure of that substantially similar to that found in the patient's blood and a bicarbonate concentration ranging from 20 to 30 mEq/L and a weak acid concentration ranging from 10 to 20 mEq/L.

While the *Veech* references disclose a peritoneal dialysis solution, they do not teach or suggest a peritoneal dialysis solution having two buffer systems and that is capable of maintaining the acid-base balance in a long term dialysis patient. In fact, the *Veech* references do not even address the problem of metabolic acidosis in patients suffering from end stage renal failure. The bicarbonate and weak acid ranges taught by *Veech* (0-55 mmole/l) are too broad and cover too many inoperative solutions that would result in metabolic acidosis or metabolic alkalosis if used for long term peritoneal dialysis solutions.

Further, the composition of *Veech* could not be used commercially because the composition is not stable during heat sterilization. In the United States, FDA regulations require heat sterilization of peritoneal dialysis solutions.

Hence, the *Veech* references do not teach or suggest a peritoneal dialysis solution capable of maintaining the acid-base balance in a long term peritoneal dialysis patient.

To supplement the *Veech* references with respect to its lack of teaching in terms of carbon dioxide partial pressure, the Patent Office again relies upon the *Zander* reference. However, *Zander*, like the *Veech* references, fails entirely to teach or suggest a composition with the buffer qualities or the ability to maintain the acid-base balance in a patient that is achieved by the example shown at Example 1 at pages 9-10 of the present application. The specific composition in *Zander* set forth at column 2 fails to disclose the use of a weak acid. The composition disclosed in column 6 of the *Zander* reference requires a weak acid concentration in the form of acetate that is too high and dangerous to use. Accordingly, one skilled in the art would be clearly discouraged upon reviewing the *Zander* reference in its entirety and would not be motivated to combine it with the *Veech* reference.

Further, the data presented in Dr. Martis' Declaration, see Exhibit B, establishes the criticality of the claimed ranges and the unexpected results of using the claimed ranges vis-à-vis the ranges taught by commercially available prior art solutions. Even when the claimed range falls within the range taught by a prior art reference, the claim range limitation is entitled to patentable weight if the range limitation is critical and unexpected results are demonstrated. *In re Waymouth*, 182 U.S.P.Q. 290, 292-93 (CCPA 1974). Here, Dr. Martis' Declaration

establishes the requisite criticality and unexpected results when the dialysis solutions of the present invention are utilized.

Therefore, as noted above, *Zander* does not teach or suggest a peritoneal dialysis solution capable of maintaining the acid-base balance in a patient. Further, any combination of *Zander* and either of the *Veech* references would result in a dialysis solution with too high of a weak acid concentration leaving to metabolic alkalosis. Accordingly, no combination of *Veech*, *Veech 2*, and *Zander* teaches or suggests the dialysis solution required by independent Claims 1, 6, 10 and 11. Therefore, Applicants respectfully request that the rejection of Claims 1-16 under 35 U.S.C. § 103 be withdrawn.

For the foregoing reasons, Applicants respectfully request reconsideration of their patent application and earnestly solicit an early allowance of same.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend Claim 6 as follows:

6. (Amended) A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4
Magnesium (mEq/L)	0.0-4
Bicarbonate (mEq/L)	[20.0-3] 20.0-30.0
Weak acid (mEq/L)	10.0-2

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; αketoglutarate; succinate; fumarate; malate; and oxaloacetate, the solution having a carbon dioxide partial pressure that is less than 60 mmHg.

Please amend Claim 10 as follows:

10. (Amended) A peritoneal dialysis solution comprising:

Dextrose (hydrous) (g/dl)	1.5-4.2
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4.0
Magnesium (mEq/L)	0.0-4.0
Bicarbonate (mEq/L)	[20.0-30.] 20.0-30.0
Weak acid (mEq/L)	10.0-20

wherein the weak acid is at least one acid chosen from the group consisting of: lactate; pyruvate; citrate; isocitrate; cis-aconitase; αketoglutarate; succinate; fumarate; malate; and oxaloacetate, and

the solution has a carbon dioxide partial pressure that is substantially similar to the carbon dioxide partial pressure of a normal subject's blood and the solution has a pH of approximately 7.0 to about 7.4.

Please amend Claim 11 as follows:

11. (Amended) A method for correcting metabolic acidosis in a dialysis patient suffering or likely to suffer from same comprising the step of:

administering to a patient a peritoneal dialysis solution that has a bicarbonate level and carbon dioxide partial pressure that are substantially similar to that found in the patient's blood wherein the solution comprises:

Dextrose (hydrous) (g/dl)	1.5-4
Sodium (mEq/L)	100-140
Chloride (mEq/L)	70-110
Calcium (mEq/L)	0.0-4
Magnesium (mEq/L)	0.0-4
Bicarbonate (mEq/L)	[20.0-3] <u>20.0-30.0</u>
Weak acid (mEq/L)	10.0-2

Bernadette Faller

LOSS OF ULTRAFILTRATION IN CONTINUOUS AMBULATORY PERITONEAL DIALYSIS: A ROLE FOR ACETATE

Bernadette Faller
and
Jean-Francois Marichal

ABSTRACT

A retrospective analysis of the ultrafiltration (UF) capacity of patients treated by continuous ambulatory peritoneal dialysis since 1978 showed that in all 31 patients using acetate-buffered dialysate the UF decreased whereas it decreased in only two (14%) of 14 patients using lactate dialysate. Prolonged exposure of the peritoneum to acetate dialysate seems to be responsible for this loss of UF.

One of the major functional features of the peritoneal membrane is ultrafiltration capacity. This enables it to maintain water balance in patients with end-stage renal disease (ESRD) treated by continuous ambulatory peritoneal dialysis (CAPD). Ultrafiltration (UF) is achieved with dialysis solutions containing a high glucose concentration, which are hyperosmolar to body fluids (1). Commercially available solutions contain glucose concentrations ranging from 82 mmol/l to 233 mmol/l. In 1981 we reported that ultrafiltration decreases over the years so that CAPD patients have to use a higher percentage of hypertonic exchanges to maintain their water balance (2). Loss of UF was defined as progressive reduction of water removal with a certain dialysis solution and for the same dwell-time.

This paper reports the evolution of the loss of the UF capacity in CAPD patients and attempts to define certain causes for this complication.

PATIENTS AND METHODS

From May 1978 to July 1983, 60 unselected patients were trained for CAPD: 34 males, 26 females aged 14 to 82 (average 52.8) years. Their residual kidney function (endogenous creatinine clearance) varied from zero to 5 (average 2.10) ml/min with a daily urine volume ranging from zero to 1650 (average 400) ml; nine patients were anuric. Our study is based on 45 of these 60 patients in whom we have complete data. Their underlying renal disease is shown in Table I.

The average duration of CAPD for the whole group was 15.1 months. For those patients still on treatment, the duration of CAPD ranged from three to 49 (average 19) months. Nineteen patients (11 males, eight females, mean age 50.3 years) have been treated for more than two years; 12 for two to three years; five for three to four years, and two for 49 months.

DIALYSIS TECHNIQUES

Implantation of the catheter: All patients had an indwelling Oreopoulos-Zellerman permanent silicone peritoneal catheter implanted surgically. After the operation, a three-day continuous peritoneal dialysis was performed with a half-automated peritoneal dialysis (PD) machine instilling progressively higher dialysate volumes. This immediate post-operative period is followed by five 12-hour sessions of intermittent PD. The dialysate used is buffered by acetate (3,4) and available in 10 litre plastic containers (Laboratoire Dubernard, Bordeaux, France).

TABLE I: *Underlying renal disease in 45 patients*

CHRONIC GLOMERULONEPHRITIS	18
DIABETIC N.	10
SYSTEMIC LUPUS N.	1
POLYARTERITIS NODOSA	1
INTERSTITIAL N.	5
NEPHROSCLEROSIS	4
HEREDITARY N.	5
UNKNOWN	1

Dialysis devices: Two types of dialysis devices used are described in Tables II and III. Thirty-one patients (607 patient months) used bags and tubing sets made by Laboratoire Aguettant (Lyon, France); Fourteen patients (275 patient months) used bags and tubing sets made by Laboratoire Travenol (Plaisir, France). One patient used both. Table IV shows the type of dialysis solution used by the 19 patients treated for more than two years.

CAPD technique: All patients performed daily CAPD with two-liter exchanges. Forty patients exchanged four times/day, two, three times/day and three, five times/day.

Treatment of peritonitis: This treatment has always been done with acetate-buffered solutions in 10-litre containers or two-litre bags. From May 1978 to January 1981, the patients were treated with a continuous peritoneal lavage until negative dialysate cultures were obtained on three consecutive days. The peritoneal lavage was performed with a half-automated PD machine with antibiotics added to the dialysate. From January 1981 to January 1983, the lavage time was reduced to 12 hours followed by CAPD with six

Key words: Continuous ambulatory peritoneal dialysis, ultrafiltration, acetate dialysate, lactate dialysate

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TABLE II: *Characteristics of the two types of CAPD material used in this study*

		AGUETTANT	TRAVENOL
Dialysat	Buffer	Acetate	Lactate
	pH	6.5	5.5
Container		PVC	PVC
Sterilization of the Bags		110°C for 60 minutes	121°C for 60 minutes
Tubing Set		Silicone	PVC
Connection Site		Polycarbonate Heat Welding	Polyester Heat Welding

TABLE III: *Dialysate composition*

		AGUETTANT		TRAVENOL	
Sodium	mMol/l	130		132	
Calcium	mMol/l	1.75		1.75	
Magnesium.....	mMol/l	0.75		0.75	
Acetate	mMol/l	35.00			
Lactate	mMol/l			35.00	
Chloride	mMol/l	97.25		102	
Glucose	mMol/l	83	220	82.5	233
Osmolality	mOsm/l	348	485	347	486

TABLE IV: *Number of patients treated for more than two years by acetate or lactate dialysate*

DURATION OF CAPD	ACETATE DIALYSATE	LACTATE DIALYSATE	ACETATE AND LACTATE DIALYSATE
2–3 years	7	6	—
more than 3 years	4	1	1

daily exchanges. Since January 1983, we have used the technique of peritoneal lavage described by Williams *et al* (5).

Measurement of UF: Peritoneal water transfer was estimated by weighing of the effluent bags and substracting from it the weight of the unused bags (6). Once a month, each patient was asked to record the osmolality of the dialysis solutions used, the diffusion times and the weight of the effluent bags used over one day.

Statistical analysis: For most variables the significance of the differences between groups of patients, were evaluated with the unpaired "t" test for small series. At 36 months of treatment, statistical analysis was impossible because there was only one patient in the lactate group.

RESULTS

Loss of UF: Patients are divided into two groups according to the buffer of the dialysis solution: Group A includes 31 patients dialysed with acetate containing solutions; of these 31 patients, 11 have used acetate-dialysis solutions for more than two years. Group B includes 14 patients dialysed with lactate containing solutions; of these 14 patients, eight have used lactate-dialysis solutions for more than two years. Figures 1 and 2 show the mean drainage volumes for isotonic (82 mmol glucose/litre) and hypertonic (233 mmol glucose/litre) dialysate dwelled for the same period according to the buffer and the duration of CAPD.

Lactate dialysate: At the initiation of CAPD (14 patients), after a four-hour dwell-time, two litres of hypertonic dialysate remove 938 ± 167 ml (mean ± standard deviations) of excess body water; at 24 months (eight patients), the volume ultrafiltered was maintained at 900 ± 173 ml. With isotonic dialysate, the ultrafiltration reached 234 ± 120 ml per two litres at the initiation of CAPD and 120 ± 125 at 24 months. However a loss of UF was noted in two of 14 patients. The first a woman with systemic lupus nephropathy, had had an inadequate UF since the initiation of CAPD and the drainage volume with an hypertonic lactate dialysate never exceeded 150 ml. In the second the decrease in UF developed progressively: at the beginning of CAPD, this patient had an UF of 1000 ml with an hypertonic exchange which decreased to only 300 ml at 36 months.

Acetate dialysate: At the beginning of CAPD (31 patients) two litres of hypertonic dialysate, after a four-hour dwell-time, removed 760 ± 160 ml of body water; after 24 months (11 patients), 332 ± 235 ml; at 36 months (four patients) 200 ± 173 ml. With isotonic dialysate, UF reached 217 ± 100 ml at time 0; at 24 and 36 months, UF was "negative" i.e. 87 ± 99 ml and 150 ± 141 ml were absorbed.

At the beginning, at one year and at two years the differences in UF with hypertonic dialysis solution between the acetate and the lactate groups were statistically significant ($p < 0.001$). With isotonic solutions, the differences between the same groups were not statistically significant at the initiation of CAPD, but became significant ($p < 0.001$) at 12 and at 24 months.

Glucose concentration in drained dialysate: In 10 patients treated for more than two years, we measured the glucose concentration in the hypertonic effluent after a four-hour dwell-time by the hexokinase enzymatic technique. In the five patients using lactate, the mean concentration was 46.9 ± 4.73 mmol/l, while in the five patients using acetate, it was 40.37 ± 7.37 mmol. This difference was not statistically significant.

Incidence of peritonitis: The 45 patients had 76 episodes of peritonitis – rate of one episode per 11.6 patient-months. In the 19 patients who were on CAPD for more than two years, the rate was one episode every 15 months. Five patients (three using lactate, two using acetate) had no peritonitis; none of the patients had more than five episodes. Among those on CAPD for more than two years, the peritoneal infection rate per patient year according to the dialysate buffer used is 0.72 episode with

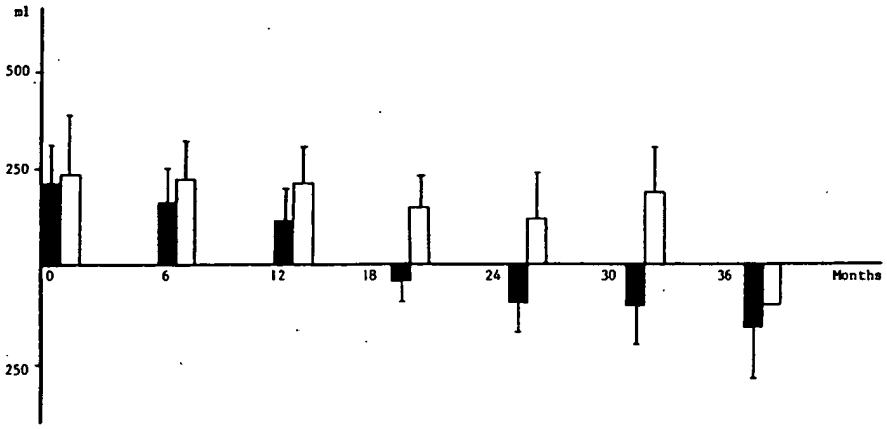

Figure 1: *Drainage volumes with isotonic dialysate. Acetate* ■; *Lactate* □.

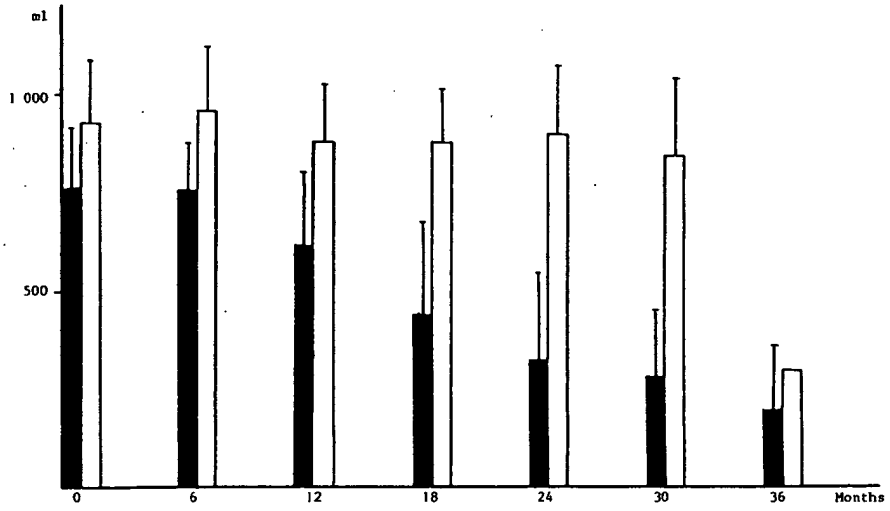

Figure 2: *Drainage volumes with hyper tonic dialysate. Acetate* ■; *Lactate* □.

TABLE V: *Biochemical measurements performed in these 45 CAPD patients*

	STARTING CAPD (45 PATIENTS)	24 MONTHS (19 PATIENTS)	40 MONTHS (3 PATIENTS)
Urea .. mMol/l	22.8 ± 8	17.3 ± 5	19.3 ± 3
Creatinine .. mMol/l	743 ± 200	849 ± 290	787 ± 170
Potassium .. mMol/l	4.4 ± 0.7	4.4 ± 0.6	4.4 ± 0.1
Bicarbonate.. mMol/l	22.6 ± 4.5	24.5 ± 1.6	24.6 ± 2.0
Hematocrit .. %	27.8 ± 5	32 ± 5	32 ± 2
Protein .. g/l	66 ± 9	65 ± 5	68 ± 2
Albumin .. g/l	36 ± 5	37 ± 4	34 ± 2
Calcium .. mMol/l	2.34 ± 0.09	2.46 ± 0.09	2.36 ± 0.07
Phosphorus.. mMol/l	1.22 ± 0.19	1.35 ± 0.18	1.33 ± 0.17

lactate dialysate and 0.85 episode with acetate dialysate. The distribution of the organisms were: Gram positive 71.5%, gram-negative 23%, fungus 2%, aseptic 3.5%. We did not observe multiple-organism peritonitis. In 11 of 76 episodes, the symptoms persisted for more than one week and we had to remove the peritoneal catheter. The organisms in these 11 episodes were: *staphylococcus epidermidis* (two), *staphylococcus aureus* (six), gram-negative organisms (three). Of these 11, seven (four diabetics) used acetate dialysate and the catheter was replaced after a lavage time ranging from three to 23 days (average 11 days). The remaining four used lactate dialysate; The catheter was replaced after an acetate lavage period ranging from three to 56 days (average 23 days). It is interesting to note that in the woman in whom the catheter was changed after 56 days of lavage with acetate, peritonitis (due to *staphylococcus epidermidis*) persisted and she was transferred to hemodialysis. Three months later, she developed sclerosing peritonitis. Since the beginning of CAPD, this patient had very low UF; she is one of the two patients with poor UF in the lactate patients' group. The other patient with progressive loss of UF with lactate dialysate had five episodes of peritonitis in 42 months on CAPD. The continuous lavage with acetate, which was used in each episode, lasted from 12 hours to four days (average two days) except in one episode of pseudomonas peritonitis, which lasted for 19 days and required catheter replacement.

We had to stop CAPD because of persistent peritonitis in two patients – the woman (already mentioned) who developed sclerosing peritonitis, and another who had previous history of abdominal surgery.

Blood chemistries: Analysis of the parameters of chronic renal failure shows stable results over time on CAPD (Table V). Serum protein and albumin were maintained at low – normal levels.

DISCUSSION

The reduction of the UF capacity of the peritoneal membrane in intermittent PD was reported by Tenckhoff in 1977 (7) and by Oreopoulos in 1981 (8) – each in a few cases. This problem is more frequent among CAPD patients – 15% of patients (9). Earlier we showed that, in our group, the UF capacity of the peritoneum has decreased progressively in 73.3% of patients. A retrospective clinical study of our patients treated by CAPD since 1978 showed that these patients fell into two groups according to the degree of UF loss.

The main difference between these

two groups was the type of dialysis solution buffer; in fact, 12 of the 14 patients using lactate-buffered dialysis solution showed no reduction of UF with hypertonic dialysis solution and only a slight loss with the isotonic solution. The two patients with impaired UF in this group represent 14.3% of the lactate group. This proportion compares with that cited by other groups using lactate (9,10). All 31 patients in the group using acetate-buffered dialysis solutions showed a progressive decrease in UF. The reduction in the drainage volumes occurred with both isotonic and hypertonic dialysis solutions. The acetate solutions were used because they were the first to become commercially available. In addition, vasodilator (11) and bacteriostatic (12) effects, which were demonstrated later, made them more attractive than the solutions containing lactate.

The duration of the CAPD treatment, and the duration of the peritoneum's exposure to acetate-containing solutions seems to play an important role in the loss of UF. Though acetate dialysis solutions have been used in all patients after the implantation of the catheter and in all peritonitis episodes, a severe reduction of UF capacity has been observed only when CAPD was carried out with acetate solutions. The prolonged use of acetate-buffered dialysis solutions seems to be particularly harmful to the peritoneal UF capacity.

Peritonitis – the risk of which depends on the duration of CAPD, could also induce alterations of the peritoneum (13). However two patients treated for more than three years with acetate dialysis solutions showed a reduction of UF without ever having had peritonitis. Under the same conditions – duration of treatment and absence of peritonitis, three patients using lactate showed no loss of UF. Moreover the patients treated for the longest period show a lower peritonitis rate than the group as a whole.

The suspected mechanism behind loss of UF is a rapid dissipation of the osmotic gradient (14). Canaud (15) showed that the UF volume depends on the ratio between the osmolality of the dialysis solution and the osmolality of the plasma. The most important quality of the peritoneal membrane is its ability to prevent the decrease in the osmotic gradient. It has been asserted that a higher peritoneal permeability to the osmotic agent caused a loss of UF (14,1). However, in our experience, after two years of CAPD, the glucose concentration in the effluent of acetate or lactate hypertonic exchanges is not significantly different. This data shows that the mechanism of loss of UF still is not clear. Verger (10,16) showed that patients with low UF have an hypermeable peritoneal membrane and a patchy or total destruction of the peritoneal mesothelium. Our patients have not had peritoneal biopsies. The dissipation of the osmotic gradient may be the result of toxicity of acetate, or of an unknown component(s) of the solutions.

To maintain water balance in the presence of loss of UF, patients have to reduce their water and salt intake and then avoid any increase in the use of daily hypertonic dialysate. However, if they use more hypertonic exchanges, especially when they don't have residual diuresis, patients are also asked to follow a low-carbohydrate diet. These dietary restrictions enabled 29 of our 31 acetate-treated patients to continue CAPD, even though all of them show a decrease in UF. One of these 31 patients is being maintained on CAPD with the addition of two monthly sessions of UF with hemodialysis.

In conclusion, the loss of UF can be ascribed to the prolonged exposure of the peritoneum to the acetate-buffered dialysis solutions. Although other factors such as unknown components of the fluids remain to be defined, we have stopped the use of these solutions in our CAPD program.

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